GH Therapy In Children

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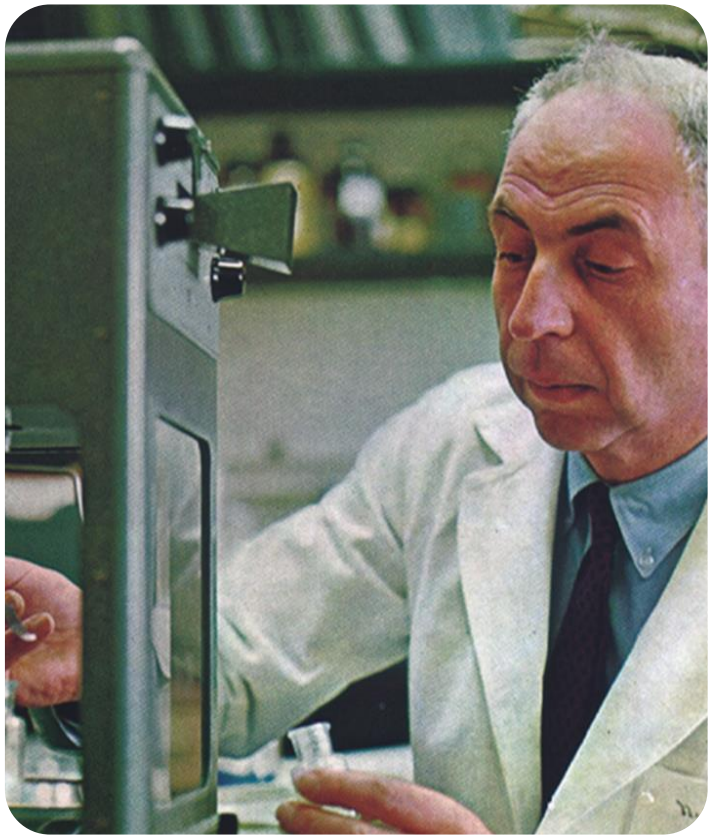
Background

- Lessons learned since recombinant human GH was introduced to the market in 1985
- Unprecedented level of scrutiny has lasted more than 35 years because of:
  - Jacob Creutzfeld disease relationship to *pituitary-derived* GH
  - Potential association between GH & leukemia
- GH was the second recombinant protein brought to market

Maurice Raben
(January 23, 1915 – September 21, 1977)

- Injected the first patient with pituitary hGH in January 1957
- The result was published in JCEM in 1958
- Today's management of children who are short and who grow better with injections of human GH derives directly from Maurice Raben's studies more than 60 years ago



Raben MS. J Clin Endocrinol Metab 1958;18: 901-3

- Initially, growth hormone was injected intramuscularly.
- In mid 1980s, it was shown as effective when administered as a subcutaneous injection.
- Early in its use, growth hormone was administered twice weekly; this was increased to 3 times weekly when the higher frequency was shown to result in an increased growth response
- 6-7 injections per week were shown to yield an even better growth response than administering injections 3 times per week
- Daily administration is now the recommended use

Growth Hormone Replacement

- Improves linear growth
- Body composition changes producing a reduction in total and visceral fat and increase in lean body mass
- Improvement in CV function and lipids
- Improves Quality of life
- Increases bone mineral density
- Improves memory, alertness, and concentration

- GH administration improves growth rate, suggesting the so-called pulsing message of GH to its target cells.
- Nocturnal administration mimics physiological GH secretion may add to efficacy.
- The effect of GH wanes with time.
- First year of treatment usually produces the greatest growth increment .
- Seasonal variation in growth rate during GH therapy, with peaks in the summer and nadirs in the winter has also been described.

GH & Puberty

- Question of whether GH replacement dosages should be increased during puberty
  - In one study, doubling the dosage of GH during puberty did not significantly change growth rate, but did tend to advance pubertal maturation
  - On the other hand, a larger randomized trial showed that an increase in dosage to 0.7 mg/kg/week (in contrast to conventional dosage recommendations of 0.18–0.35 mg/kg/week) improved growth rates, and height SDS without evident adverse effects

GH Therapy

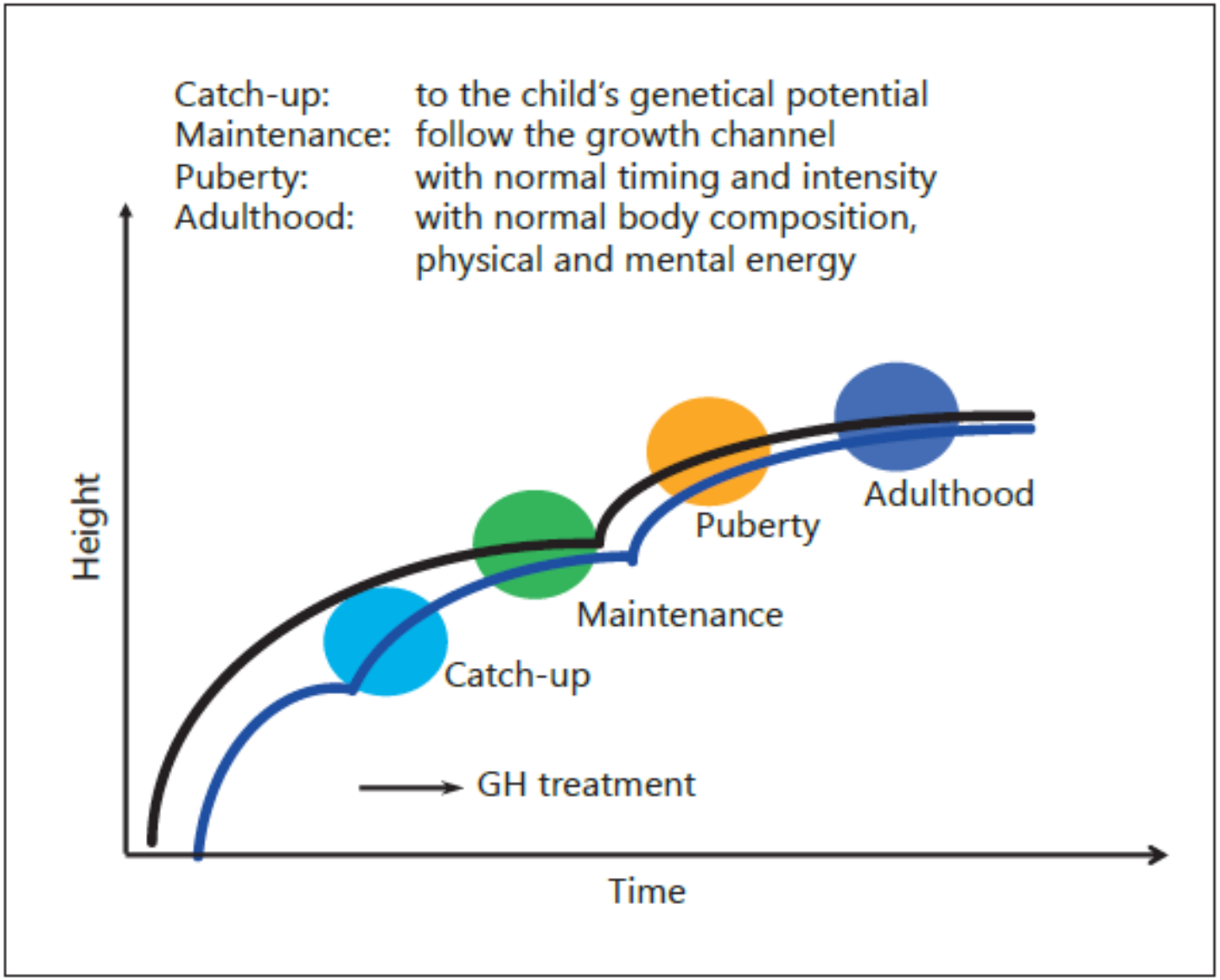
- Children treated with GH may experience transient or persistent declines in serum thyroxin (T4) levels
  - in approximately 25%, T4 levels become abnormally low and may impair response to GH
  - Thyroid function tests should be monitored periodically (especially early) during GH therapy to ensure detection of secondary T4 deficiency and prevent this treatable cause of a poor response to GH
- Cortisol supplementation may also impair the growth response to GH; as little as 7.5–10 mg/day of hydrocortisone may be growth-suppressive in a school-aged child
- When ACTH deficiency has been documented, the dosage of daily cortisol replacement therapy should be reduced to a level sufficient to prevent symptoms of fatigue and lack of energy

Year of initial FDA approval	Indications for GH treatment
1985	Pediatric growth hormone deficiency
1993	Growth failure secondary to chronic renal failure up to the time of renal transplantation
1996	Adult growth hormone deficiency
1996	HIV wasting in adults
1996	Turner syndrome
2000	Prader-Willi syndrome
2001	Small for gestational age
2003	Idiopathic short stature
2003	Short bowel syndrome
2006	*SHOX* gene deficiency
2007	Noonan syndrome

FDA indications of Growth Hormone Therapy

- Growth hormone deficiency
- Chronic renal failure
- Turner Syndrome
- Prader-Willi Syndrome
- SGA
- Idiopathic short stature
- AIDS wasting
- Noonan Syndrome
- Chronic diseases
- Skeletal dysplasia (Achondroplasia)
- Others

Targets of GH Therapy



Albertson Wikland, Horm Res 2012

Effects of GH Therapy in Children

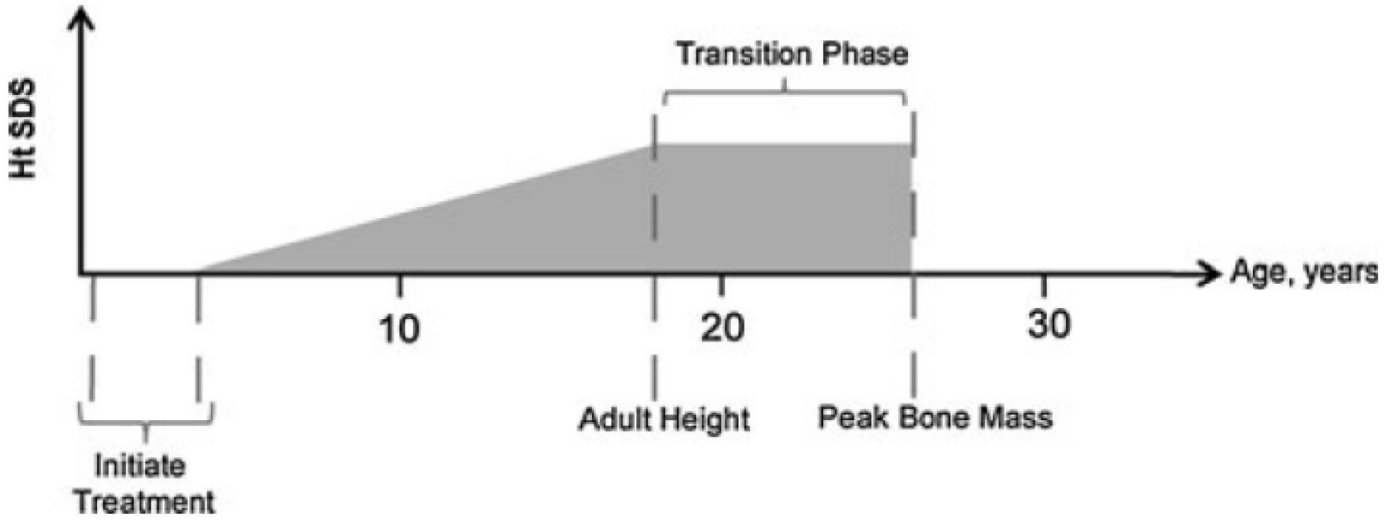


Fig. 1 Outcomes of growth hormone (GH) treatment for patients with GH deficiency (GHD). After initiation of treatment, prepubertal children show increases in height SD score (Ht SDS) over time. GH treatment is usually terminated when adult height is attained (normally in late adolescence to early adulthood). Patients with reconfirmed GHD may continue GH therapy. Peak bone mass is usually attained by approximately 25 years of age

Cook DM et al, Pituitary 2012

GH Therapy

- The recommended GH dose is calculated based on body weight & vary according to specific condition (i.e. dose of GHD is different from that of CRF or ISS).
- In case of GHD, treatment with GH should be initiated early & be monitored by a pediatric endocrinologist every 3–6 months in order to:
  - verify growth velocity.
  - identify possible side effects.
  - titrating the GH dose by measuring IGF-1 & using prediction modules !!).
  - Checking for patients compliance (adherence).

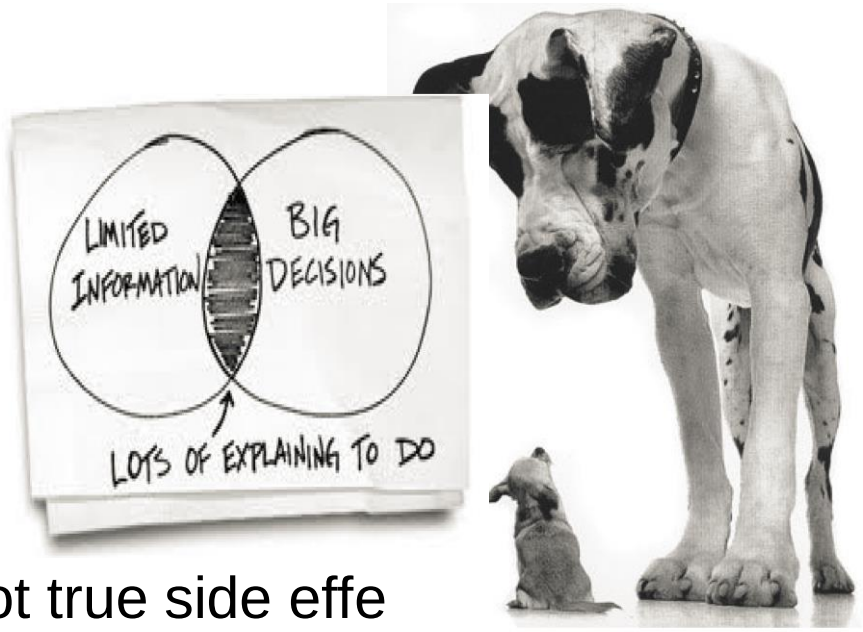
Challenges in GH Therapy

- Growth hormone deficiency (GHD) is one of the most important endocrine treatable causes of short stature.

- Variability in response to treatment from one child to another has been observed in the clinical practice & documented in many studies due to several endogenous & exogenous factors.

Factors influencing the response to GH?

- Indication of GH therapy (GH Deficiency, Turner Syndrome, SGA…).
- Age of starting GH therapy.
- Pubertal status.
- GH dose.
- GH dose titration 3-6 monthly.
- Treatment adherence.
- Birth Weight (SGA).
- Concomitant medication.
- Associated co-morbidity.
- Rarely, development of GH ar
- Cultural believes (spreading not true side effe
- Family education and uncertain worries on side effects
- Limited parents information on GH therapy.



- Optimization of GH therapy is a prime challenge in the treatment of GHD.
- It requires evaluation of the response of an individual to the therapy.
- To analyze or predict the probable amount of growth that can be expected during treatment, researchers have developed prediction models.
- The second important challenge which limits the effectiveness of GH therapy is patient adherence.
- A literature search has found several studies which identified that poor adherence is the major factor that reduces the effectiveness of GH therapy

Growth Hormone Deficiency (GHD)

- The administration of GH to treat children with short stature resulting from GHD or GH insufficiency has now accrued over 35 years of clinical experience.
- GH is absolutely indicated in this condition.
- Efficacy demonstrated in large international databases with growth velocity in first year of therapy of 8-10 cm.

Growth Hormone Deficiency (GHD)

- Recommend a dose in the range of 0.025–0.05 mg/kg/day
- Under special circumstances, higher doses may be required, including adolescents with late diagnosis and diminished period of time for catch-up growth.
- Recently it has been proposed that IGF-1-based GH dosing may improve growth responses.

Idiopathic Short Stature

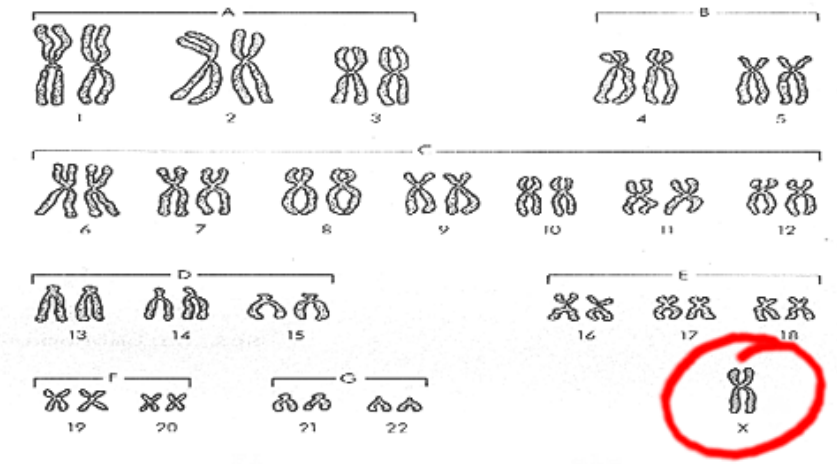
- 2003 FDA approval
- GH can increase their adult height by 4-7 cm
- Information regarding the efficacy of GH in improving the final height of children with idiopathic short stature (ISS) is now accumulating
- the most effective GH therapy will require substantial growth acceleration prior to puberty

GnRH & GH therapies

- Novel approaches to the treatment of idiopathic short stature include concomitant suppression of pubertal hormones using GnRH agonist therapy and reduction of estrogen production using aromatase inhibitors
- study reported that combined gonadotropin releasing hormone agonist/growth hormone (GnRH/GH) therapy for 3 years resulted in gains in predicted height of 8–10 cm without demonstrable side effects
- Final height data on these patients are not yet available, and current expense of such treatment is formidable

Turner's Syndrome

- Evidence of IGF-1 resistance
- Haploinsufficiency of one copy of SHOX gene
- Absence of normal pubertal estrogen induced increase in endogenous GH secretion



Turner's Syndrome & GH

- Untreated mean final height of these patients is 143 cm , approximately 20 cm below average of the corresponding ethnic group
- Initiation of GH therapy is recommended as soon as a patient with TS has dropped below the 5th percentile of the normal female growth curve
- This may be as early as 2 years of age
- For girls below 9–12 years of age, the recommended starting dosage is 0.05 mg/kg/day, although individualization of dosing is appropriate based upon response

Noonan syndrome

- Is an autosomal dominant disorder that shares clinical features with TS, including growth retardation usually in the absence of GH deficiency.
- A recent 3 year controlled trial showed a mean increase in growth rate from a baseline of 4.4 cm/year to 8.4, 6.2, and 5.8 cm/year during years 1, 2, and 3 of GH therapy respectively.
- Others report that initial GH-induced growth acceleration is followed by a waning of effect with long-term therapy; in a small group of 10 patients, a mean increment in final height of only 3.1 cm was observed.

SGA (fail to catch up growth)

- Definition
  - Birth weight below 10 % for gestational age
  - Birth weight or length at least - 2 SD < mean.
- 85-90% catch up growth in the 1st or 2nd year of life.
- Remaining 10-15% are eligible for GH treatment.

SGA & GH

- Approved by the FDA as an indication for GH therapy.
- Higher-dose GH therapy has also led to hyperinsulinemia in some of these children .
- Continuation of these clinical trials until final height will be required to determine the safety and efficacy of GH for IUGR.
- Given the accelerated tempo of puberty in these patients, concomitant administration of GnRH analog or Aromatase inhibitors to permit a longer period of growth may be indicated for severely height-disabled individuals with IUGR.

CRF & GH

- Poor nutrition, anemia, and chronic metabolic acidosis contribute to the growth failure
- Elevated GH level, exaggerated responses to provocative stimuli, depressed serum IGF-1 levels, and increased levels of IGF-1 binding protein (in particular IGFBP-1) suggest resistance to the action of GH
- A randomized, double-blind, placebo-controlled study of 125 prepubertal growth-retarded children with CRF revealed first-year (10.7 ± 3.1 cm/yr) and second-year (7.8 ± 2.1 cm/yr) growth rates in the GH-treated group that were significantly greater than those seen in the placebo group
- In general, responsiveness to GH appears to be inversely related to the degree of renal function impairment and metabolic compromise
- Growth failure due to CRF is an approved indication for GH therapy

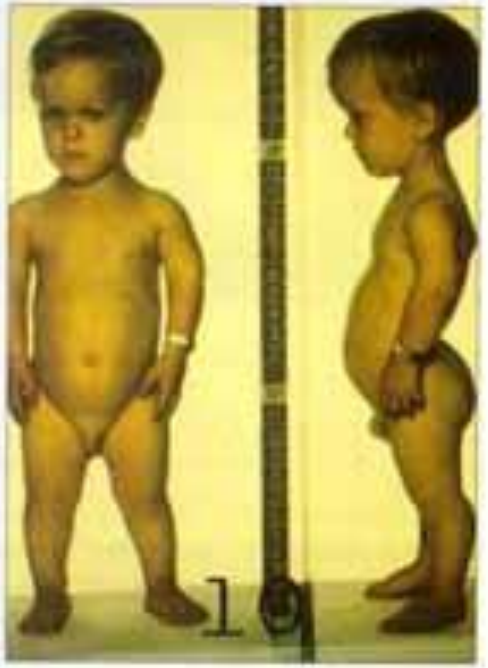
Hypophosphate Rickets & GH

- Consequently, GH has been administered to poorly growing children with X-linked hypophosphatemic rickets
- In a recent study reporting final height outcome, GH therapy combined with conventional treatment resulted in a change in height SD score in six children with XHR (mean baseline −3.4, mean post-treatment, −2.4) whereas no change in height SD score was observed in six XHR patients not treated with GH
- Phosphate retention, bone markers, and radial bone mineral density increased only in the GH-treated group
- Additional long-term studies are needed to verify the value of long-term GH therapy for patients with this disorder

Achondroplasia

- Autosomal Dominant Disorder.
- Affects about 1 in 25,000 people.
- About 98% of those with Achondroplasia have a point mutation in the FGFR3 gene at 4p16.3 that encodes fibroblast growth factor receptor 3.

124A and 124B Note the large head with prominent forehead.

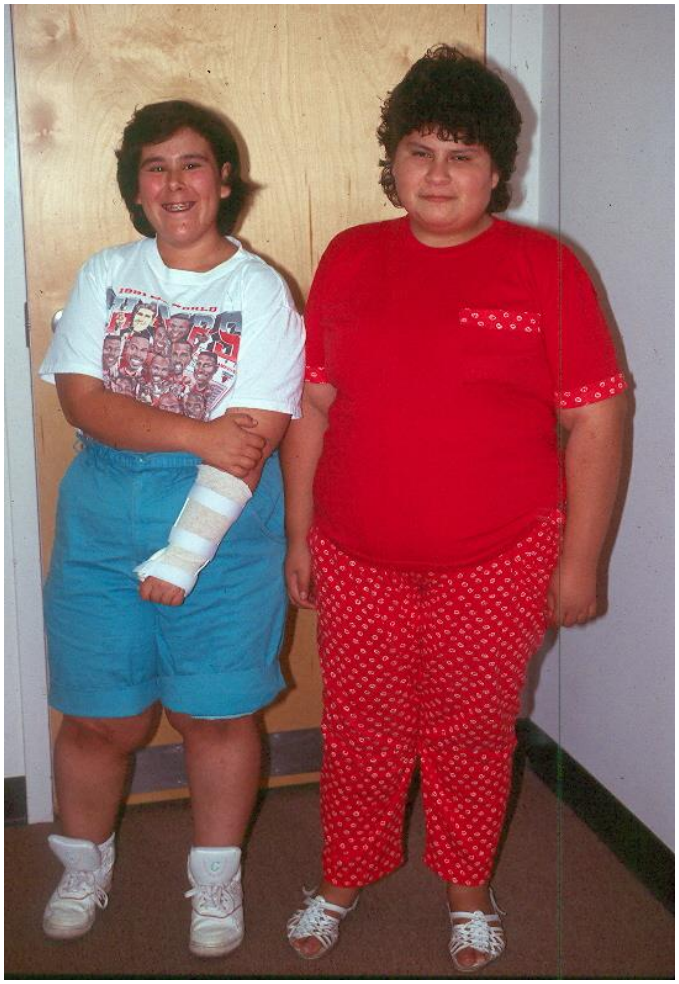


Skeletal dysplasia & GH

- Growth response to GH is generally less than that observed in children treated for classic GH deficiency and declines after initial acceleration
- Reports of response to GH are variable
- Some data indicate little change in growth rate, even when higher than conventional dosages are used
- More recent studies suggest that GH therapy can increase growth rate and height z-score in a dose-dependent manner without significant side effects
- Effects on ultimate height remain unknown

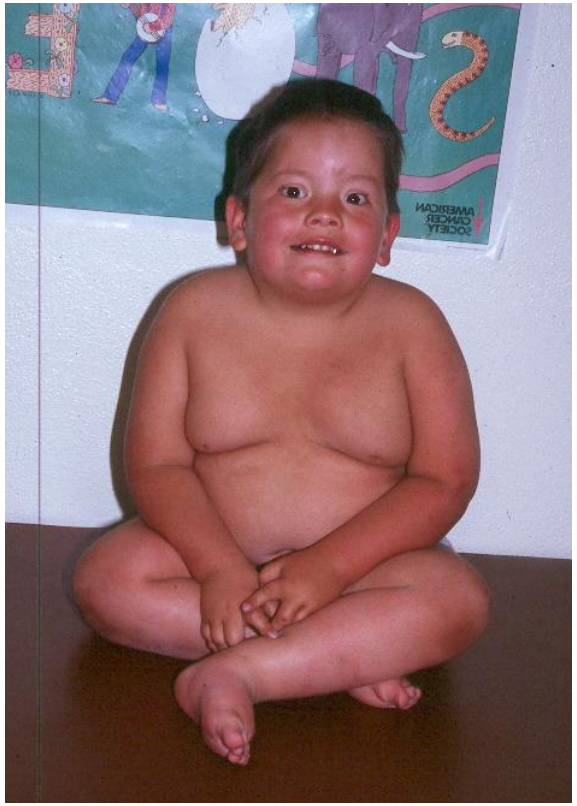
Prader-Willi Syndrome

- 1/15,000 births
- Neonatal hypotonia & cryptorchidism
- Hypothalamic dysfunction: lack of satiety & subsequent obesity; low sex hormones & growth hormone deficiency
- Cognitive & behavioral differences
- Cause is lack of expression of paternal genes at 15q11-13



Prader-Willi Syndrome at Different Ages

Infancy: hypotonia, feeding problems, cryptorchidism, apnea, check adrenals



Childhood: obesity, apnea oppositional behaviors, learning problems, short stature Rx GH and thyroid, check adrenals

Adulthood: type 2 DM, obstructive sleep apnea, hypogonadism Rx hormone replacement

Prader-Willi Syndrome

- Primary hypothalamic dysfunction leads to GH deficiency and obesity
- GH treatment of these children increases height velocity &lean body mass and decreases adiposity
- Sudden death-2003 FDA patient safety news
- 7 fatalities world wide in pts being treated with Genotropin for Prader-Willi syndrome.

GH risks/benefits to body composition in PWS

- Body mass index in children with Prader-Willi Syndrome during human growth hormone therapy
- Whether GH affects body mass and composition in patients with PWS in a clinic setting remains unclear and may reflect yet undiscovered individual-specific characteristics.
- It is, however, important to remind parents that GH is not a cure for obesity and that control of food access and increased physical activity remain the most important factors in obesity control

Adverse side effects of GH therapy

- Recombinant biosynthetic GH preparations are highly purified and free of contaminants
- The possibility of viral transmission through GH has been virtually eliminated
- Antigenicity of GH preparations is also low, although GH antibodies can be detected in 10–30% of treated children. With rare exceptions (less than 0.1%), these antibodies do not impede effects of GH

GH Replacement & Cancer Risk

- Patients with previous malignancies or history of radiation therapy carry significant risk for recurrence and second malignancy.
- Recommend measurement of serum IGF-I levels in patients receiving GH treatment; place of regular IGFBP-3 monitoring is not defined.
- Recommend that IGF-I level be maintained within appropriate age- and gender-related normal range in GH-deficient adults during long-term therapy.

Safety - GH Therapy in Children
Malignancy Risk

- Certain patient groups who receive GH treatment carry an intrinsic risk of developing malignancies, including those with Neurofibromatosis type 1, Fanconi anemia, Downs and Bloom syndromes.
- Although no evidence that GH replacement poses increased cancer risk, *such children be carefully monitored* with regard to tumor formation.

Safety - GH Therapy in Children
Glucose Metabolism

- Diabetes mellitus is not contraindication to GH treatment in children
- Diabetic care should follow standard clinical practice

GH Treatment and Intercurrent Illness

- No data to support discontinuation of GH replacement treatment during illness.
- Risk of hypoglycemia should be considered in children with GH deficiency who discontinue GH treatment.

Safety - GH Therapy in Children

Issues related to GH treatment in patients with non-GH deficient disorders

- Monitoring glucose homeostasis in Turner syndrome and glucose homeostasis and lipid profiles in chronic renal failure should be undertaken at intervals determined by standard clinical practice
- In patients with chronic renal failure treated with GH who receive renal transplant, assessment of graft function and surveillance for development of malignancy should be carried out according to routine nephrology guidelines

Adverse effects of GH treatment

- In first 8 weeks – Benign Intracranial Hypertension.
- Has been reported in 1 in 1000 children receiving GH treatment.
- due to the increase in salt and water retention.
- complain of headache, loss of vision, nausea or vomiting.
- resolves rapidly when growth hormone treatment is stopped
- GH can usually then be restarted at a lower dose, and the dose slowly increased without further problems.

Adverse effects of GH treatment

- Peripheral edema
- Carpal tunnel syndrome
- Arthralgia & Myalgia
- Slipped capital femoral epiphysis (SCFE)
  - Children with GHD require close monitoring for the symptoms of SCFE, most commonly pain in the hip or knee, or a limp
- In children with scoliosis, the degree of the scoliosis may get worse when growth is accelerated with growth hormone treatment.

Adverse effects of GH treatment

- GH excess reduces insulin sensitivity, and given the trend toward higher dosages, it is important to assess a GH dosage's effect on carbohydrate metabolism

- Recent report of an increased frequency of type 2 diabetes in childhood GH recipients was surprising

Is GH mitogenic ??

- In 1988, reports from Japan describing leukemia in GH-treated children raised concern about malignancy
- Any possible increased incidence of leukemia appears limited to those patients with known risk factors, and due to the small numbers of events in such patients, it remains impossible to determine any contribution of GH therapy
- With regard to non-leukemia cancers, a retrospective analysis of large post-marketing database found no evidence of an increased risk of developing an extra cranial, no leukemia neoplasm in GH-treated patients

Is GH mitogenic ??

- No reports have associated GH therapy with an increased incidence of tumor recurrence
- A lack of reliable knowledge about the natural history of recurrence of these tumors, however, supports a cautious interpretation of such data.
- Most recurrences occur within the first 2 years of treatment, and most endocrinologists defer institution of treatment until a year of stable remission has passed.
- No study to date has directly compared the incidence of new second tumors in those receiving GH

Conclusions

Growth hormone therapy has advantages including:

- Improves linear growth
- Body composition changes producing a reduction in total and visceral fat and increase in lean body mass
- Improvement in CV function and lipids
- Improves Quality of life
- Increases bone mineral density
- Improves memory, alertness, and concentration

Conclusions

- GH has been approved for many conditions including: growth hormone deficiency, CRF,
- Turner Syndrome, PWS,SGA, ISS, AIDS wasting and Noonan Syndrome.
- Increased frequency of GH administration improves growth rate, suggesting the so-called pulsing message of GH to its target cells .
- Nocturnal administration mimics physiological GH secretion may add to efficacy .
- The effect of GH wanes with time.
- First year of treatment usually produces the greatest growth increment .

Conclusions

- Certain patient groups who receive GH treatment carry an intrinsic risk of developing malignancies, including those with Neurofibromatosis type 1, Fanconi anemia, Downs and Bloom syndromes.
- Although no evidence that GH replacement poses increased cancer risk, *such children be carefully monitored* with regard to tumor formation




Thanks